
Standardized Allergenic Extracts Derived From Mammals

John L. Ohman, Jr, and Bo Sundin

It is difficult to write a definition of standardized extracts that would produce widespread agreement among clinical allergists and immunologists. Ideally a standardized extract should contain measured amounts of all of the major allergens. A major allergen would be defined as an allergen that gives rise to IgE antibody in a majority of clinically sensitive patients and that is present in a high enough concentration in the environment to cause disease. In addition, the concentration and cumulative dose of such allergens that induce a positive reaction in the skin of clinically sensitive subjects and a beneficial response on immunotherapy should be known. The above ideal is not even approximated with most mammalian allergens. Nevertheless, we will attempt to summarize what is known and then develop recommendations that should guide in the preparation and use of extracts that have been characterized to some extent. This will be done with the full realization that future research will require modification of these recommendations.

Historical Review and Epidemiology

One of the first recognized cases of animal dander hypersensitivity was described by the Italian physician Pietro Mattioli. In 1570 he described a patient who was so sensitive to cats that if he was sent into a room in which a cat was concealed he could detect its presence by the occurrence of symptoms that included agitation, diaphoresis, and pallor.¹ Three centuries later, Salter² recognized a relationship between exposure to animals and the occurrence of asthma and described certain asthmatics that "cannot stroke or nurse a cat" or "go near a rabbit hutch."

Cats and dogs are the most common household pets in urban areas. In Scandanavia and the United States cats and dogs are present in up to 50% of households.^{3,4} A number of studies from different parts of the world have documented immediate skin test reactions to cat and dog allergens in 20-30% of unselected patients with asthma. Most of these studies have documented a higher prevalence of sensitization to cat allergens than to dog allergens.⁵⁻¹³ A study from Sweden showed that 60% of children with asthma had evidence of allergy to animals.³ Vanto and Koivikko⁴ have shown that 40% of asthmatic

Address correspondence and requests for reprints to John L. Ohman, MD, Associate Clinical Professor of Medicine, Tufts University School of Medicine, Boston, MA 02115.

children in Finland have a positive prick test to dog dander extract despite minimal contact with dogs in most instances. In asthmatic patients, the presence of a cat or dog in the environment has more relation to the severity of the asthmatic symptoms than a number of other factors, such as air pollution.¹⁴

The prevalence of cat or dog allergy in a general population is not known with certainty, but there is some similarity of estimates from different parts of the world. The overall prevalence of animal allergy in Sweden is estimated at about 5%.³ Positive prick test reactions to dog allergen are seen in 14% of unselected adolescents in Finland.¹ The prevalence of cat allergy in the general population can be estimated from data generated by the Tuscon Epidemiological Study of Obstructive Lung Disease.¹⁵ In a carefully selected population sample the overall prevalence of prick test reactions to a cat epithelial extract was 19.9%. If we assume that 25% of those individuals that are prick test positive are also clinically sensitive, we can estimate the number of cat-sensitive individuals in the United States at 10 million. Most of the above studies were carried out with minimally characterized extracts.

In rural areas, allergy to horses, cows, and other farm animals can be a serious occupational problem. Exposure to allergens from such animals may not always be apparent because hair from horses and cows may be used in mattresses, stuffed furniture, and carpets.

Laboratory animal allergy is common in research facilities where the incidence of allergic disease has been consistently reported to be about 15%. This makes animal allergy an occupational hazard of major importance in such locations.¹⁶⁻²¹ Even primates have been implicated in allergic reactions in research facilities.²² Rodent allergy may be important in houses infested with rats and mice.²³

Collection of Material and Extraction

Mammalian allergens present particular problems in selection of source materials. Since the 1920s, the dander or particles from the pelt have been assumed to be the vector causing human inhalant allergy. It is for this reason that the starting material for almost all commercial mammalian allergen is still whole pelt, skin scrapings, or hair.

Very early in the study of allergens it was recognized that serum also contained allergens. Initial reports of serum allergens dealt mainly with horse serum because in many instances sensitization seemed to occur by therapeutic administration of antitoxin.²⁴⁻²⁶ The role of serum allergens in the causation of inhalant allergy has remained poorly defined, but interest in these allergens was stimulated by the fact that serum components including albumin could be found in extracts of epithelium.^{24,25,27-30} Allergenic activity now has been described in the serum of cats, dogs, laboratory animals, and a number of other species.^{19,29,31-35} Serum has never gained wide acceptance as a material to use for diagnosis or for immunotherapy in inhalant allergy. There are many obvious reasons for this. Even though serum components are present in epithelial extracts, a patient is not exposed to serum as such. It is probable that serum contains a very unrepresentative relative concentration of allergenic components as well as a large quantity of irrelevant protein. The di-

agnostic specificity of serum allergens has long been unclear. A number of analytical approaches have demonstrated that serum allergens of different species share antigenic sites.^{27,33,36-39} Therefore, a positive skin test reaction to serum allergens of one species may derive from primary sensitization to another species.

There have been a number of reports, mostly in the last 15 years, dealing with allergens in urine,^{29,40-45} and saliva.^{19,43,46-48} These findings add a considerable amount of uncertainty in the selection of the best source material to use for diagnosis and treatment. Certainly both urine and saliva have the potential to become airborne in particulate form and could very well be important in inhalant allergy. In one study of cat allergens it was shown that urine and serum contain no unique allergens that are not also present in extracts of pelt or saliva.⁴⁹

The major allergen in cat allergy, cat allergen 1, is excreted in saliva^{43,49} but also may be produced by structures in the pelt.⁵⁰ The above data suggest that epithelial sources are likely adequate as a source of allergen in the domestic cat. Surface washes of living cats provide a rich and renewable source of cat allergen 1 as well as a small amount of albumin, and such washes have been suggested as a useful source of clinically relevant allergen.⁵¹ Cat washes do not contain measurable amounts of several minor allergens defined by the crossed-radioimmuno-electrophoresis technique (CRIE) in cat pelt extracts.

In a recent study of rat allergens derived from urine, saliva, and skin using CRIE, unique minor allergens were found in each of these sources.⁴⁸ This raises the possibility that a mixture of allergens derived from different sources might be advisable in some species. It should be pointed out that in most species, including the rat, mouse, and cat, there remains a limited number of major allergens. The imposition of a requirement that extracts contain all minor allergens is probably not realistic or even advisable. This is particularly true when a minor allergen is defined by weak activity in a technique such as CRIE, which is difficult to standardize because of its dependency on the nature of polyspecific rabbit antisera and human serum pools. It is to be anticipated that in most mammalian species the pelt extract will contain more allergens than extracts of hair or epithelial scrapings. In this context "more" is not to be automatically considered "better."

There is increasing evidence that in the rat, mouse, and possibly the guinea pig that the urine is the primary source of the major allergens.^{20,29,35,41,42,52-57} Skin test reactivity to mouse and rat urine appears to have diagnostic value, although there remain a few subjects that appear to be clinically sensitive who do not react to at least some urine specimens.³⁵

In horse allergy, most of the evidence suggests that extracts of dander and not the serum contain most of the relevant allergens.⁵⁸⁻⁶² There are no studies of horse urine.

In cow allergy using the CRIE technique, 11 allergens have been described, most of which appear to be of epithelial origin. Some cow allergens also are found in saliva, urine, and serum.^{63,64} Some evidence exists for cross reactivity of antigens derived from the cow and those of the sheep, goat, and swine.⁶⁴

With dog allergy, most studies have used the epithelial extracts that contain albumin as well as several other lower molecular weight allergens.^{6,27,38,39,46,65-68} A few studies have mentioned the presence of allergenic

activity in dog urine^{45,69} or saliva,⁴⁶ although the value of these sources is simply not known. Breed-specific allergens have frequently been alleged on the basis of casual studies of individual extracts,⁷⁰⁻⁷² although when dog extracts are analyzed carefully no breed-specific allergens have yet been found.^{27,38,39}

A knowledge of the general properties of mammalian allergens provides some guidance as to the way they should be extracted from source material and handled after extraction. All mammalian allergens described to date appear to be acidic proteins with a molecular weight range between 15,000 and 160,000. Extraction conditions should be at an ionic strength of 0.1–0.2 and at a pH of above 7.0 (preferably 7.5) for maximum solubility of allergens. Extraction should be carried out for 12–24 hours at cool temperatures (ie, 5–10°C) with the optional addition of bacteriostatics and proteolytic inhibitors to avoid degradation. It has been our experience that during the process of extraction of pelts the extracting fluid undergoes a marked drop in pH that necessitates the addition of alkali to maintain a pH at above 7.0. If pelts are used, vigorous washing before extraction will probably remove a major amount of significant allergen.⁷³ Dialysis of the resulting extracts with retention of proteins above 10,000 is probably advisable. Additional purification to remove high molecular weight materials (above 200,000) could be carried out without risk of major loss of allergenic activity. Defatting of the starting material may improve extraction efficiency and should not be associated with any disadvantages.

Characterized Mammalian Allergens

For the purpose of this discussion, a characterized allergen will be defined as an allergen whose antigenic properties are defined by a polyclonal or monoclonal antiserum and has been studied by at least 2 analytical procedures to determine its charge and size properties. A complicating feature in the study of allergens is the common occurrence of multiple forms of single allergens that share antigenic sites as defined by heterologous antiserum. These multiple forms, or isoallergens, usually differ with respect to charge. The demonstration of shared antigenic sites in a family of isoallergens is usually accomplished by the use of polyspecific heterologous antiserum and various immunoelectrophoretic procedures, as in the case of cat allergen 1 and the mouse urinary allergen.^{74,75} It is to be anticipated that monoclonal antibodies will aid in the definition of antigenic sites on allergen molecules, although their absolute specificity may be a limitation in that single epitopes on a given molecule also may be present on other unrelated molecules. The extensive use of crossed-immunoelectrophoresis (CIE) and CRIE has greatly aided in overall descriptive studies of antigens and allergens in crude extracts. The limitations of these techniques are many. They are cumbersome to use when trying to quantitate individual allergens in extracts of widely varying antigen content or when attempting to track individual allergens during sequential purification. Each polyspecific rabbit antiserum has its own pattern of antibody specificity, and it is difficult to compare different rabbit antisera directed against the same crude extract. In CRIE, the human serum pool also is difficult to standardize and contains greatly varying levels of IgE antibody against the

individual allergens. The relative intensity of the radiographic image is dependent on subjective assessment, on the nature of the rabbit antiserum, and on the number of antigenic sites available in the immune precipitate. Uptake of radioactivity in precipitin arcs in the CRIE may be nonspecific⁴¹; therefore, the careful use of control subjects is required.

Cat allergen 1, which has a molecular weight of 35,000 daltons and an isoelectric point of 3.85,⁷⁵ is the major allergen in the domestic cat. It has been fairly well characterized by the use of a monospecific, polyclonal rabbit antiserum.⁷⁶ Absorption with this antiserum removes most of the allergenic activity (as defined by skin test and radioallergosorbent test (RAST)) in pelt extracts and a variety of commercial extracts.^{28,76} In a random survey of allergy clinic patients, it was shown that IgE antibody to cat allergen 1 correlated with clinical sensitivity much better than IgE binding to cat serum, crude cat pelt, or purified cat albumin.⁷⁷ The content of cat allergen 1 in a variety of cat extracts reliably predicts the skin test reactivity of these extracts in a population of cat-allergic individuals.^{28,47} The importance of cat allergen 1 also is confirmed by the CRIE technique.^{63,73} The ability to reliably measure cat allergen 1 by techniques such as quantitative immunoelectrophoresis has allowed a comparison of concentrations of this allergen in different cat products. This allergen can be found in cat saliva, extracts of epithelium, and in surface washes of living cats.^{43,51} Serum and urine contain either unmeasurable or very low and inconsistent amounts of cat allergen 1.^{43,49} It has been suggested that saliva is the primary source of cat allergen 1 and that this would be a useful source of allergen.⁷⁸ There is evidence that cat allergen 1 is associated with the sebaceous glands of the skin as well as the sublingual salivary glands.⁵⁰ It has been pointed out that the viscous physical characteristics of saliva make it unattractive as a practical source of allergen.⁶² The quantity of allergen that can be obtained per saliva collection (40 to 80 U)⁴³ is much lower than what can be obtained with a brief surface wash of a cat,⁵¹ which usually yields more than 800U. One unit is approximately equal to 2 µg protein.

Serum albumin can be readily identified in many mammalian extracts and can be shown to occasionally give rise to IgE-antibody binding in the cat,^{33,49} dog,^{27,65,79} mouse,⁵³ rat,³⁷ and horse.⁸⁰ In none of these species has albumin been shown to give rise to IgE-antibody binding in a high proportion of allergic individuals.^{39,61,77} There is evidence for allergenic cross-reactivity of albumins of different species.^{33,81}

A single allergen in mouse urine seems to be a predominant allergen in mouse allergy.^{53,54,74} This allergen has a molecular weight of 16,000 to 18,000 daltons and an isoelectric point of 4–5. It is the predominant protein in mouse urine and appears to be identical to the mouse urinary protein complex described by Finlayson et al in 1965.⁸² This protein is synthesized predominantly in the liver and excreted in large quantity in the urine. Structural genes of this protein are located on chromosome 4,⁸³ and the synthesis of this group of proteins is stimulated by androgen.⁸⁴

In the rat there appears to be a urinary allergen similar to that found in the mouse with a similar molecular weight and a highly negative charge.^{41,85} In an important study using the CRIE technique in 14 rat-sensitive patients, it was found that a major allergen in fur, urine, and saliva was identical to

this urinary "prealbumin" allergen.⁴⁸ A number of other minor and less characterized allergens were described in this study.

In the dog, a number of partially characterized allergens have been described with molecular weights that range from 28,000 to above 70,000.^{38,39,65,79}

Practical Data: Safety and Efficacy

The treatment of choice for the majority of patients allergic to animal danders is avoidance. For patients for whom avoidance is impossible and pharmacologic therapy is insufficient, immunotherapy may be an alternative. Initial experience with immunotherapy using uncharacterized animal dander extracts in uncontrolled protocols has given contradictory results regarding the efficacy of this treatment.⁸⁶⁻⁸⁸ The following 4 studies document the efficacy of immunotherapy when well-characterized cat or dog allergens are used.

The first report of immunotherapy in cat-induced asthma using an extract of standardized allergen content in a double-blind study was published by Taylor and Ohman.⁸⁹ Asymptomatic subjects with normal pulmonary function were selected for a double-blind trial of immunotherapy with cat pelt extract. The cat pelt extract (CPE 149) contained measured amounts of CAT 1, and cat albumin, as well as other uncharacterized allergens, on CRIE. The patients had a history of asthma on exposure to cats, a positive prick test reaction to cat pelt extract, and a positive bronchial challenge. Patients were randomly assigned to active treatment or placebo groups and received weekly or biweekly injections over a 3-4 month period. The 5 patients on active treatment received a cumulative dose of cat extract that ranged from 16.4-44.8 mg of total solid containing 1.7-4.7 mg of CAT 1, and 5.3-14.6 mg of cat albumin. Mild systemic reactions occurred in 3 patients in the active and 3 patients in the placebo group. The patients with active treatment showed a reduction in skin reactivity to cat pelt extracts as well as a significant mean reduction in bronchial sensitivity. Bronchial response to histamine did not change significantly. In the placebo group no changes occurred. Vigorous IgG-antibody responses were seen in both cat allergen 1 and cat albumin.⁹⁰ One patient who had received a cumulative dose of several hundred micrograms of albumin developed precipitating antibody to albumin. This suggests that the concentration of albumin in the immunizing mixture should be reduced.

In another double-blind study by Ohman,⁹¹ the efficacy of immunotherapy in cat-induced asthma was studied using a purified fraction of cat pelt extract that contained only the 2 allergens CAT 1 and cat albumin. Nine active- and 8 placebo-treated subjects completed a 16-week treatment schedule. The active treatment group received a mean cumulative dose of 10.9 U of CAT 1. Active treatment resulted in significant reduction in prick test reaction and bronchial sensitivity. The treatment also resulted in a significant delay of the onset of ocular and pulmonary symptoms on exposure to live cats. IgG to CAT 1 and cat albumin increased as well. No change was observed in bronchial responsiveness measured by methacholine challenge, and no significant change in basophil sensitivity to CAT 1 was observed. No changes were observed in the placebo group for any of the above-mentioned parameters.

Table 1. Controlled Trials of Immunotherapy in Animal Dander Allergy

Trials	1	2	3	4	5
Species: cat 1, dog 2, mouse 3, rat 4, other 5	3,4,5	1	1	1,2	2
Blinded treatment and evaluation	—	+	+	+	+
Beneficial change in <i>in vitro</i> parameters					
IgG antibody	+	+	+	+	nd
WBC histamine release	nd	nd	—	nd	nd
<i>In vivo</i> parameters					
bronchial challenge	nd	+	+	+	—
conjunctival challenge	nd	nd	nd	nd	+
skin test titer	nd	+	+	+	nd
Clinical evaluation	+	nd	+	+	nd
References	94	89,90	91	92	93

nd = not done

+ = beneficial response

— = no beneficial response

In the above study, the concentration of cat allergen 1 that produced a 3-mm wheal by prick test ranged from 0.0013–1.33 U/mL.⁹¹ For use in prick tests, extracts should probably contain approximately 2 U/mL of cat 1. Concentrations of cat albumin above 50 µg/mL in such preparations are probably unnecessary.⁶²

In a double-blind study from Scandinavia using partly purified and standardized extracts,⁹² 40 patients with asthma on dog or cat exposure were assigned to either the active- (dog or cat) or placebo-treatment group. After 1 year of treatment the code was broken. Twenty-two patients were found to belong to the active group (15 cat and 7 dog) and 18 patients to the placebo group. The cat-treated group had received 42 µg^{13–65} of CAT 1. In this group the bronchial sensitivity and prick test reactions were reduced significantly ($p < .001$). Also, increased bronchial tolerance for histamine was found in the cat treated group ($p < .005$). In the dog-treated group there was also an increased tolerance to histamine and allergen, but the changes were not significant. In the placebo group no changes occurred. Mild systemic reactions occurred 15 times in the active- and 7 times in the placebo-treatment group. These reactions responded promptly to treatment.

In a Finnish double-blind study⁹³ 27 asthmatic children allergic to dog were treated with a commercial standardized aluminum hydroxide-bound dog extract or placebo. After 1 year of therapy the conjunctival sensitivity to dog dander extract had decreased significantly ($p < .001$) in the active-treated group. The decrease in bronchial sensitivity was not significant. No systemic reactions occurred.

One additional non-blinded study of immunotherapy in lab animal allergy has been done,⁹⁴ and clinical improvement was subjectively reported. In addition, blocking antibody responses were demonstrated which were specific for the antigen used.

As shown in these 5 studies, immunotherapy with standardized cat and dog extracts appears to be a viable alternative treatment for allergic individuals in cases where avoidance or pharmacologic therapy is impossible or insuffi-

cient (Table 1). Although serious reactions have not been observed in any of the studies to date, trained personnel and proper equipment should be available to handle any anaphylactic responses that may occur after immunotherapy treatments. Provided that these precautions are taken, immunotherapy is a safe alternative in the treatment of allergic disease (Table 1).

References

1. Pharmacia: Footnotes on Allergy. Uppsala, Sweden, 1980
2. Salter HH: On asthma. London, Churchill, Ltd., 1864
3. Kjellman B, Petterson R: The problem of furred pets in childhood atopic disease. *Allergy* 38:65-73, 1983
4. Vanto T, Koivikko A: Dog hypersensitivity in asthmatic children. *Acta Paediatr Scand* 72:571, 1983
5. Sarsfield JK, Boyle AG, Rowell EM, et al: Pet sensitivities in asthmatic children. *Arch Dis Child* 51:186-189, 1976
6. Bryant DH, Burns MW: Skin-prick test reactions to inhalant allergens in asthmatic patients. *Med J Aust* 1:918-924, 1976
7. British Thoracic Society, Research Committee of: Skin tests and clinical features of asthma. *Brit J Dis Chest* 69:125-136, 1974
8. Murray AB, Ferguson AC, Morrison BJ: The frequency and severity of cat allergy vs. dog allergy in atopic children. *J Allergy Clin Immunol* 72:145-149, 1983
9. Rudolph R, Kunkel G, Blohm B, et al: Zur Häufigkeit und Klinischen Bedeutung von Allergien gegen Tierepithelien. (Frequency and clinical significance of sensitization to animals.) *Allergologie* 4:230-236, 1981
10. Gutman AA, Patterson R (ed): Allergic diseases. Diagnosis and management. Philadelphia, JB Lippincott Co., 1972
11. Muljano ES, Voorhorst R: Atopy to dander from domestic animals. *Allerg Immunol* 24:50-60, 1978
12. Holley JW, Willen K: *Acta Allergol* 24:284-293, 1969
13. Pauli B, Bessot JC, Hirth C, et al: Dissociation of house dust allergies. A comparison between skin tests, inhalation tests, specific IgE and basophil histamine release measurements. *J Allergy Clin Immunol* 63:245-252, 1979
14. Kurata JH, Glovsky MM, Newcomb RL, et al: A multifactorial study of patients with asthma. Part 2: Air pollution, animal dander and asthma symptoms. *Ann Allergy* 37:398-409, 1976
15. Barbee RA, Brown GB, Kaltenborn W, et al: Allergen skin-test reactivity in a community population sample: Correlation with age histamine skin reaction and total serum Immunoglobulin E. *J Allergy Clin Immunol* 68:15-19, 1981
16. Lincoln TA, Bolton NE, Garret AS: Occupational allergy to animal dander and sera. *J Occup Med* 16:465-469, 1974
17. Rajka G: Ten cases of occupational hypersensitivity to laboratory animals. *Acta Allergol* 16:168-176, 1961
18. Lutsky II, Neuman I: Laboratory animal dander allergy. I. An occupational disease. *Ann Allergy* 35:201, 1975
19. Lutsky I, Toshner D: A review of allergic respiratory disease in laboratory animal workers. *Lab Anim Sci* 28:751-756, 1978
20. Schumacher MJ, Tait BD, Holmes MC: Allergy to murine antigens in a biological research institute. *J Allergy Clin Immunol* 68:310-318, 1981
21. Gross NJ: Allergy to laboratory animals: Epidemiologic, clinical and physiologic aspects, and a trial of cromolyn sodium in its management. *J Allergy Clin Immunol* 66:158-165, 1980
22. Petry RW, Voss MJ, Kroutil LA, et al: Monkey dander asthma. *J Allergy Clin Immunol* 75:268-271, 1985
23. Snyder RD, Kahan SA: Rodent hair sensitivity in asthmatic children. *Ann Allergy* 29:113-117, 1971

24. Tuft L: Further studies in serum allergy. VI. Antigenic relationship between horse dander and horse serum sensitivity. *J Allergy* 6:25–38, 1934
25. Squire JR: The relationship between horse dandruff and horse serum antigens in asthma. *Clin Sci* 9:127–150, 1950
26. Walker IC: Studies on the sensitization of patients with bronchial asthma to the different proteins found in the dandruff of the horse and in the hair of the cat and the dog and to the sera of these animals. *J Med Res* 35:497–503, 1917.
27. Blands J, Lowenstein H, Weeke B: Characterization of extract of dog hair and dandruff from six different dog breeds by quantitative immunoelectrophoresis. *Acta Allergol* 32:147–169, 1977
28. Ohman JL, Jr, Lowell FC, Bloch KJ, et al: Allergens of mammalian origin. V. Properties of extracts derived from the domestic cat. *Clin Allergy* 6:419–428, 1976
29. Cockcroft A, Edwards J, McCarthy P, et al: Allergy in laboratory animal workers. *Lancet* i:827–830, 1981
30. Osvath P Endre L: Immunanalytischer Vergleich zwischen Kuhhaarextrakten und anderen Rinder- und Mulchproteinen. 2. Immunelektrophoretische Untersuchungen. *Allerg Immunol* 17:63–68, 1971
31. Ohman JL, Jr: Allergy in man caused by exposure to animals. *J Am Vet Med* 172:1403–1406, 1978
32. Wodehouse RP: Immunochemical studies of the proteins of cat hair. *J Immunol* 2:227–235, 1917
33. Ohman JL, Jr, Bloch KJ, Kendall S, et al: Allergens of mammalian origin. IV. Evidence from common allergens in cat and dog serum. *J Allergy Clin Immunol* 57:560–68, 1976
34. Markussen B, Lowenstein H, Weeke B: Allergen extract of horse hair and dandruff. Quantitative immunoelectrophoretic characterization of the antigens. *Int Arch Allergy Appl Immunol* 51:25–37, 1976
35. Beeson MF, Dewdney JM, Edwards RG, et al: Prevalence and diagnosis of laboratory animal allergy. *Clin Allergy* 13:433–442, 1983
36. Arbesman CE, Beede RB, Rose NR: Sensitivity to animals. A case report with immunologic studies. I. Clinical aspects. *J Allergy* 29:130–138, 1958
37. Wahn U, Peters T, Siraganian RP: Studies on the allergenic significance and structure of rat serum albumin. *J Immunol* 125:2544–2549, 1980
38. Brandt R, Yman L: Dog dander allergens. Specificity studies based on the radioallergosorbent technique. *Int Arch Allergy Appl Immunol* 61:361–370, 1980
39. Wuthrich B, Guerin B, Hewitt BE: Cross-allergenicity between extracts of hair from different dog breeds and cat fur. *Clin Allergy* 15:87–93, 1985
40. Lutsky I, Fink JN, Kidd J, et al: Allergenic properties of rat urine and pelt extracts. *J Allergy Clin Immunol* 75:279–284, 1985
41. Longbottom JL: Purification and characterization of allergens from the urines of mice and rats In Oehling A (ed): *Proceedings of the International Symposium of Allergology and Clinical Immunology*, Jerusalem, 1979. Oxford, Pergamon Press 1980, pp 483–490
42. Edwards RG, Lee D, Beeson MR, et al: The development and validation of radioallergosorbent tests for the detection of specific human IgE antibody directed against laboratory animal urinary proteins. *Int Arch Appl Immunol* 71:53–58, 1983
43. Brown PR, Leitermann K, Ohman JL, Jr: Distribution of cat allergen 1 in cat tissues and fluids. *Int Arch Allergy Appl Immunol* 74:67–70, 1984
44. Newman-Taylor AJ, Myers JR, Longbottom JL, et al: Immunological differences between asthma and other allergic reactions in laboratory animal workers. *Thorax* 36:229 (Abstract), 1981
45. Hoffman DR: Dog and cat allergens: Urinary proteins or dander proteins? *Ann Allergy* 45:205–206, 1980
46. Spain WC, Gillson RE, Strauss MB: Comparative immunologic studies with salivary and epithelial extracts of the dog, cat and rabbit., *J Allergy* 13:563–573, 1942
47. Baer H, Anderson MC, Turkeltaub PC: Comparison of the relative potency of cat allergens determined by cat 1 content and parallel line skin test assay. *J Allergy Clin Immunol* 71(Suppl):160, 1983

48. Walls AF, Longbottom JL: Quantitative immunoelectrophoretic analysis of rat allergen extracts II. Fur, urine and saliva studied by crossed radioimmunoelectrophoresis. *Allergy* 38:501-512, 1983
49. Anderson MC, Baer H, Ohman JL, Jr: A comparative study of the allergens in cat urine, serum, saliva, and pelt. *J Allergy Clin Immunol* 76:563-569, 1985
50. Bartholome K, Kissler W, Baer H, et al: Where does cat allergen 1 come from? *J Allergy Clin Immunol* 76:503-506, 1985
51. Ohman JL, Baer H, Anderson MC, et al: Surface washes of living cats: An improved method of obtaining clinically relevant allergen. *J Allergy Clin Immunol* 72:288-293, 1983
52. Newman-Taylor AJ, Longbottom JL, Pepys J: Respiratory allergy to urine protein of rats and mice. *Lancet* ii:847-849, 1977
53. Siraganian RP, Sandberg AL: Characterization of mouse allergens. *J Allergy Clin Immunol* 63:422-435, 1979
54. Schumacher MJ: Characterization of allergens from urine and pelts of laboratory mice. *Mol Immunol* 17:1087-1095, 1980
55. Levy DA: Allergenic activity of proteins from mice. *Int Arch Allergy Appl Immunol* 49:219-221, 1975
56. Pepys J: Clinical and therapeutic significance of patterns of allergic reactions of the lungs to extrinsic agents. *Am Rev Resp Dis* 116:573-588, 1977
57. Swanson MC, Agarwal MK, Yunginger JW, et al: Guinea-pig-derived allergens. Clinicoimmunologic studies, characterization, and size distribution. *Am Rev Respir Dis* 129:844-849, 1984
58. Lowenstein H, Markussen B, Weeke B: Isolation and partial characterization of three major allergens of horse hair and dandruff. *Int Arch Allergy Appl Immunol* 51:48-67, 1976
59. Lowenstein H: Characterization and chemical modification of isolated allergens from horse hair and horse dandruff. *Int Arch Allergy Appl Immunol* 57:349-357, 1978
60. Lowenstein H, Markussen B, Weeke B: Identification of allergens in extracts of horse hair and dandruff by means of crossed radioimmunoelectrophoresis. *Int Arch Allergy Appl Immunol* 51:38-47, 1976
61. Leegaard J, Roth A: RAST in the diagnosis of hypersensitivity to horse allergens. A comparison with clinical history and in vivo tests. *Clin Allergy* 7:455-464, 1977
62. Ohman JL, Jr: Selection of Source Materials for Reference Preparations, Mammalian Allergen In Fourth International Paul Ehrlich Seminar. New York, Gustav Fisher Verlag, 1985
63. Lowenstein H: Allergene von Katze, Hund, Rind und Pferd. (Allergens of cats, dogs, cows and horses.) *Allergologie* 4:265-269, 1981
64. Prahl P, Bucher D, Plesner T, et al: Isolation and partial characterization of three major allergens in an extract from cow hair and dander. *Int Arch Allergy Appl Immunol* 67:293-301, 1982
65. Yman L, Brandt R, Ponterius G: Serum albumin, an important allergen in dog epithelia extracts. *Int Arch Allergy* 44:358-368, 1973
66. Berrens L: Epidermal allergens. *Rev Allergy* 24:917-925, 1970
67. Ceska M, Ponterius G: Study of the nature of the binding sites of some allergens interacting with IgE. *Int Arch Allergy* 45:819-827, 1973
68. Moore BS, Hyde JS, Manaligod LM: A comparative study of allergens of canine origin. *Ann Allergy* 39:240-245, 1977
69. Lutsky I, Fink JN, Arkins JA, et al: Skin test reactivity to dog-derived antigens. *Clin Allergy* 10:331-340, 1980
70. Morrow Brown H, Thantrey N, Su S, et al: Rassenspezifische Allergie gegenüber Hunden. (Breed specific allergy to dogs). *Allergologie* 4:256-260, 1981
71. Hooker SB: Qualitative differences among canine danders. *Ann Allergy* 2:281-288, 1944
72. Fagerberg E, Wide L: Diagnosis of hypersensitivity to dog epithelium in patients with asthma bronchiale. *Int Arch Allergy* 39:301-309, 1970
73. Anderson MC, Baer H: Allergenicity active components of cat allergen extracts. *J Immunol* 127:972-975, 1981

74. Ohman JL, Jr, Moffat S, Lorusso JR: Properties and standardization of a major mouse allergen (Abstract). *J Allergy Clin Immunol* 73:191 (Suppl), 1984
75. Leitermann K, Ohman JL: Cat allergen 1: Biochemical, antigenic, and allergenic properties. *J Allergy Clin Immunol* 74:147–153, 1984
76. Ohman JL, Jr, Lowell FC, Bloch KJ: Allergens of mammalian origin. III. Properties of a major feline allergen. *J Immunol* 113:1668–1677, 1974
77. Ohman JL, Jr, Kendall S, Lowell FC: IgE antibody to cat allergens in an allergic population. *J Allergy Clin Immunol* 60:317–323, 1977
78. Guerin B, Hewitt B: A comparative study of allergen extracts from cat fur, cat pelt and cat saliva. *Ann Allergy* 46:127–131, 1981
79. McLean AC, Glovsky MM, Hoffman DR, et al: Identification of allergens in dog dander extract. I. Clinical and immunological aspects of allergenicity activity. *Ann Allergy* 45:199–204, 1980
80. Aronssen T, Wide L: Studies on allergens of horse epithelium with two variants of RAST. *Int Arch Allergy Appl Immunol* 47:224–241, 1974
81. Wahn U, Siraganian RP: Kreuzreaktivitat gegenüber Säugetier-Allergenen (Cross reactivity of mammalian allergens.) *Allergologie* 4:282–285, 1981
82. Finlayson JS, Asofsky R, Potter M, et al: Major urinary complex of normal mice: Origin. *Science* 149:481–482, 1965
83. Krauter K, Leinwand L, D'Eustachio P, et al: Structural genes of the mouse major urinary protein are on chromosome 4. *J Cell Biol* 94:414–417, 1982
84. Derman E: Isolation of a cDNA clone for mouse urinary proteins: Age- and sex-related expression of mouse urinary protein genes is transcriptionally controlled. *Proc Natl Acad Sci USA* 78:5425–5429, 1981
85. Walls AF, Longbottom JL: Comparison of rat fur, urine, saliva, and other rat allergen extracts by skin testing, RAST, and RAST inhibition. *J Allergy Clin Immunol* 75:242–251, 1985
86. Brown FR, Wolfe GI: Observations on animal dander hyposensitization. *Ann Allergy* 26:305–308, 1968
87. Tuft L, Torsney PT: Experience in the hyposensitization treatment of animal dander-allergic patients with alum precipitated pyridine extracts. *Am J Med Sci* 253:19–22, 1967
88. Tuft L, Torsney PJ, Kreithen H: Hyposensitization therapy with alum-precipitated pyridine extracts in animal dander sensitive patients. *Ann Allergy* 36:165, 1976
89. Taylor WW, Ohman JL, Jr, Lowell FC: Immunotherapy in cat induced asthma. Double-blind trial with evaluation of bronchial responses to cat allergen and histamine. *J Allergy Clin Immunol* 61:283–287, 1978
90. Ohman JL, Jr, March DG, Goldman M: Antibody responses following immunotherapy with cat pelt extract. *J Allergy Clin Immunol* 69:319–326, 1982
91. Ohman JL, Jr, Findlay SR, Leitermann KM: Immunotherapy in cat-induced asthma. Double-blind trial with evaluation of in vivo and in vitro responses. *J Allergy Clin Immunol* 74:230–239, 1984
92. Sundin B, Lilja G, Graff-Lonnevig V, et al: Immunotherapy with partially purified and standardized animal dander extracts. *J Allergy Clin Immunol* 77:478–487, 1986
93. Valovirta E, Koivikko A, Vanto T, et al: Immunotherapy in allergy to dog: A double-blind clinical study. *Ann Allergy* 53:85–88, 1984
94. Wahn U, Siraganian RP: Efficacy and specificity of immunotherapy with laboratory animal allergin extracts. *J Allergy Clin Immunol* 65:413–421, 1980.